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FLT3-directed therapy in acute myeloid leukemia: lessons from the final analysis of LACEWING

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Treatment options for older intensive chemotherapy (IC-ineligible) patients with newly diagnosed (ND) *FLT3*-mutated (*FLT3*^{mut}) acute myeloid leukemia (AML) have historically been limited. While hypomethylating agents (HMAs) in combination with venetoclax (VEN) have emerged as a mutation-agnostic standard-of-care for IC-ineligible patients, optimal management of ND *FLT3*^{mut} AML remains unclear. The phase III LACEWING trial was designed during a pivotal period in AML drug development, after the FLT3 inhibitor (FLT3i) gilteritinib (GILT) had demonstrated an overall survival (OS) benefit in relapsed/refractory *FLT3*^{mut} AML, but before HMA+VEN became standard frontline therapy in older or unfit patients.[1] By comparing GILT plus azacitidine (GILT+AZA) to AZA or GILT monotherapy, LACEWING sought to determine whether earlier FLT3i use could improve outcomes.

In this issue of *Haematologica*, Wang *et al.* report the final 6.5-year analysis of the phase III LACEWING trial, which evaluated GILT+AZA versus AZA or GILT monotherapy in patients with ND IC-ineligible *FLT3*^{mut} AML.[2] Beyond providing mature OS data with substantially longer follow-up than the primary report, this study includes new exploratory analyses of measurable residual disease, pharmacokinetics, emergent mutations, and outcomes within molecular subgroups.

One of the most striking findings of LACEWING is the discordance between response outcomes and survival. Despite the substantial increase in composite complete remission rates with GILT+AZA versus AZA alone (62.5% vs 28.1%), median OS was nearly identical (9.8 vs 9.2 months). Such discordance is not unique to LACEWING. In the phase II randomized AG221-AML-005 study, the addition of enasidenib to AZA significantly improved response rates in ND, IC-ineligible, *IDH2*-mutated AML, without a corresponding OS benefit.[3] Similarly, the recently reported phase III PASHA trial comparing intensive chemotherapy plus GILT versus midostaurin in ND *FLT3*^{mut} AML did not demonstrate a significant OS benefit, despite numerically improved event-free survival with GILT.[4] Collectively, these studies highlight a recurring challenge in AML drug development: meaningful improvements in response do not always translate into measurable gains in OS, particularly in this current era with multiple effective treatment options for AML patients harboring targetable mutations. Understanding the various factors that contribute to a response vs OS discordance is therefore critical for any randomized study, including LACEWING.

Firstly, treatment crossover likely attenuated any potential survival difference, as more than one-quarter of patients assigned to the AZA arm subsequently received GILT in salvage. In a post-hoc analysis, these patients experienced a median OS of nearly 14 months, substantially longer than the 7.5-month survival observed among AZA-treated patients who never received subsequent GILT. Such crossover effectively redistributed the benefits of FLT3 inhibition across treatment groups, making demonstration of an OS advantage considerably more difficult. The authors attempt to control for this in a propensity score adjusted analysis of patients who did not receive subsequent AML therapy, demonstrating a numerically longer median OS with GILT+AZA (9.0 vs 3.3 months).

Secondly, substantial biological heterogeneity exists within *FLT3* AML, and the benefit of FLT3i may not be uniform across patients. Although exploratory and limited by small numbers, patients with *FLT3*-ITD disease, particularly those with an allelic ratio ≥0.5, appeared to derive greater benefit from GILT-containing therapy. Similar trends were observed in select co-mutational subsets, suggesting that FLT3 dependence and broader molecular context may influence treatment response and survival.

Thirdly, as LACEWING was conducted before VEN-based therapy became standard, the key question today is how these findings inform treatment in the VEN era. If we examine post hoc analyses of patients with *FLT3*^{mut} AML treated with VEN+AZA vs AZA on VIALE-A,[5] response rates were comparable to GILT+AZA vs AZA (67% vs 36%) in LACEWING, yet VIALE-A also reported a median OS benefit with VEN+AZA compared to AZA (12.5 vs 8.6 months). Notably however, much of the VEN+AZA benefit may be driven by patients harboring *FLT3*-tyrosine kinase domain (TKD) mutations, whereas outcomes among *FLT3*-ITD patients receiving VEN+AZA remained poor with a median OS <12 months. Against this backdrop, the exploratory subgroup analyses from LACEWING are noteworthy, as they support the notion that highly FLT3-dependent leukemias may require more FLT3-directed suppression than can be achieved with VEN-based therapy alone.

Perhaps one of the most valuable analyses from LACEWING lies not in its efficacy data, but in the characterization of resistance and relapse. Among patients treated with GILT±AZA, more patients relapsed with *FLT3* wildtype clones compared to AZA alone (81% vs 40%). Interestingly however, nearly 40% of patients relapsing after GILT-containing regimens acquired new mutations in the RAS/MAPK signaling pathway. These findings support a growing body of evidence that adaptive signaling through downstream proliferative networks represents a major mechanism of resistance to targeted inhibitors.[6,7] How can this challenge be addressed?

One potential answer is the use of FLT3i triplet regimens. In the long-term follow up of a Phase I/II study evaluating AZA+VEN+GILT in IC-ineligible ND adults with *FLT3*^{mut} AML, the CRc rate was 96% with a 3-year OS of 46%.[8,9] Similarly, the multicenter VICEROY study reported CRc rates exceeding 90% with AZA+VEN+GILT.[10] Although there are no randomized trials of FLT3i triplets vs doublets resulted to date, these results support their ongoing investigation in both IC-ineligible and potentially also eligible patients as a bridge to allogeneic stem cell transplant.

Another strategy to address clonal complexity would be to use combination targeted therapies. For example, the frequent co-occurrence of *NPM1* and *FLT3* mutations has generated interest in combining menin and FLT3i, while concurrent *IDH1/2* and *FLT3* provide a rationale for combining FLT3i and IDHi. Preclinical data suggest that such combinations may enhance anti-leukemic activity and suppress emergence of resistant subclones, and several clinical trial combinations are in early phases at this time (NCT06769490, NCT06222580, NCT05756777, NCT07032727).

In conclusion, despite a negative primary endpoint, this final report of LACEWING

provides thought-provoking exploratory analyses that extend beyond the top headline. In the current era of VEN, the clinical role of GILT+AZA alone is limited. Nevertheless, the study provides an important foundation for future combination strategies and reinforces the importance of molecular heterogeneity, clonal evolution, and mechanisms of therapeutic resistance in *FLT3*^{mut} AML.

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Table 1. Frontline Lower-Intensity Therapy for *FLT3*-mutated AML				
Regimen	**Patient Population**	**CRc rate**	**Median OS (months)**	**Notes**
AZA (LACEWING)	ND, *FLT3*^{mut}, IC-ineligible	28.1%	9.2	Median age, 76 years, 81% ITD alone
GILT (LACEWING)	ND, *FLT3*^{mut}, IC-ineligible	54.5%	5.2	Median age, 78 years, 77% ITD alone
GILT + AZA (LACEWING)	ND, *FLT3*^{mut}, IC-ineligible	62.5%	9.8	Median age, 77 years, 77% ITD alone
VEN + AZA (VIALE-A *FLT3*$^{mu+}$ subgroup)	ND, *FLT3*^{mut}, IC-ineligible	67%	12.5	Median age 75, years, 71% ITD alone
AZA + VEN + GILT (single-center)	ND, *FLT3*^{mut}, IC-ineligible	95%	29.7	Median age, 71 years, 73% ITD alone
AZA + VEN + GILT (multi-center)	ND, *FLT3*^{mut}, IC-ineligible	90%	12-month OS 83%	Median age, 77 years, 83% ITD alone
Definition of abbreviations: AZA = azacitidine, GIL = gilteritinib, IC = intensive chemotherapy, ITD = internal tandem duplication, ND = newly diagnosed, OS = overall survival, VEN = venetoclax				